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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,738	05/26/2000	Daniel A. Vallera	11983-004001	1069

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/579,738	VALLERA ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,8,9,11,12,15,17-25,34 and 36-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8,9,11,12,15,17-25,34 and 36-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

The amendment and response filed 6/7/04 have been entered. Claims 1, 4-6, 9, 36, and 38 have been amended. Claims 43-46 are newly submitted. Claims 3 and 7 are canceled. Claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, 34, and 36-46 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 6/7/04 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The previous rejection of Claim 34 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment limiting the first member of the affinity pair to cytokines and growth factors; in view of the exhibits illustrating the levels of the skilled concerning using cytokines as targeting domain of the fusion toxin; and in view of the evidence that in addition to the intravenous route of administration disclosed in the specification, the later submitted declaration has shown that intraperitoneal and intratumoral (local) administration could also reduce tumor cell load.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended claim 36 recites "a sample of cells", the recitation appears to lack an antecedent basis in the specification. It is unclear what type of cells are included and excluded in the sample of cells, thus the metes and bounds of the claims are unclear. It is suggested to replace "a sample" with an isolated population of T lymphocytes" since the population of claim 22 is drawn to T lymphocytes as targeting cell.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of

35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 6, 9, 12, 15, 19-24, 34, 36-40, 42, 44, 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Chen et al* (Nat 1997;385:78-80), in view of *Kreitman et al* (Int J Immunopharm 1992;14:465-72), and as evidenced by *Moreck et al* (Cancer Immunol Immunother,1991;32:32-52).

Chen et al teach isolated targeting cells comprising a vector, wherein the vector comprises transcriptional and translational regulatory sequence (including a signal sequence) operably linked to a nucleic acid encoding a fusion immunotoxin protein (e.g. fig. 1A); wherein the fusion protein comprises a targeting domain, i.e. a single chain antibody with high-affinity binding to the extracellular domain of HER-2, over-expressed on various human breast and ovarian tumors; and a toxic domain comprising a toxic molecule PE40 (pCMV-e23sFv-PE40, 2nd paragraph, page 78), wherein the targeting cells are generated by transducing the plasmid vector into human MOLT-4 T lymphocytes (3rd paragraph, page 78), or by transducing a retroviral vector expressing the immunotoxin into human LAK T lymphocytes (6th paragraph, page 78); wherein the targeting cells kill tumor cells (have significant binding affinity for a cancer cell) *in vitro* (e.g. fig. 3a) or *in vivo* (e.g. figures 4As-4Be). Although not relied upon, *Moreck et al* teach that LAK cells comprises both CD4+ and CD8+ T lymphocytes (e.g. Table 7). *Chen et al* also compared the efficacy of the retroviral transduced cells expressing the immunotoxin e23sFv-PE40 with that of the e23sFv-PE40 immunotoxin itself, and teach, "TUMOR GROWTH WAS EFFECTIVELY INHIBITED BY THE TRANSDUCED CELLS BUT NOT BY DIRECT ADMINISTRATION OF THE SAME

AMOUNT OF IMMUNOTOXIN". *Chen et al* concluded that given that almost any antigen can be targeted on the cell surface, this approach should be applicable to treatment of cancer in general (right column, page 79). It is noted that the LAK cells used by *Chen et al* comprises both CD4+ and CD8+ T lymphocyte. Further, *Chan et al* clearly implied that transferring tumor-specific CTLs for cancer therapy is standard practice in the art, but because of the difficulties in obtaining sufficient amount of such cells, there is a need to provide other alternatives. The teaching of *Chen et al* differs from the instantly claimed invention in that it does not explicitly teach that cytokines and growth factors could be used as a targeting moiety.

Kreitman et al supplemented the disclosure of *Chen et al* by establishing that it is well known in the art that cytokines and growth factors could be used in the form of a fusion protein to target toxic molecules to tumor cells expressing the receptor of the cytokine or growth factor. *Kreitman et al* teach that chimeric toxins composed of a growth factor (cytokine) is an evolving alternative for targeted killing of a desired cell such as malignancy (1st paragraph, page 465), and disclose various fusion toxins comprising a toxic molecule PE40 and a targeting domain that is either a cytokine (IL-6 or IL-2) or a growth factor (TGF-alpha) or a single chain antibody (fig. 2), wherein the recombinant fusion protein is produced by a plasmid vector. *Kreitman et al* go on to teach that continuous intraperitoneal infusion of the fusion toxin sufficiently suppresses the growth of tumors in a nude mouse model (fig. 3b).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Chen et al* with that of *Kreitman et al* by substituting the single chain antibody with the cytokine or growth factor with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because given the levels of the skilled in the art and the numerous candidate cytokine and growth factor molecules available in the art, it is within the levels of the skilled to select a corresponding targeting domain depending on the target cells of interest. Moreover, given the efficacy of the fusion toxin as taught by *Kreitman et al*, and the efficacy of the transduced cells as taught by *Chen et al*, the ordinary skilled would have had a reasonable expectation of success in suppressing tumors because the transduced cells are more effective than the same amount of the fusion toxins. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 4, 8, 11, 17, 18, 25, 41, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Chen et al* (Nat 1997;385:78-80) and *Kreitman et al* (Int J Immunopharm 1992;14:465-72) as applied to claims 1, 2, 6, 9, 12, 15, 19-24, 34, 36-40, 42, 44, 46 above, and further in view of *Chan et al* (J Blood 1996;88:1445-56), and *Debinski et al* (J Bio Chem 1993;268:14065-70),.

The combined teaching of *Chen et al* and *Kreitman et al* does not explicitly teach using IL-3 and IL-4 as the targeting domain or DT390 as the toxic molecule, or treating malignant hematological disease. *Chan et al* and *Debinski*

et al supplemented the teaching *Chen et al* and *Kreitman et al* by establishing that it was well known in the art at the time of the instant filing, IL-3 and IL-4 are effective targeting molecules for the fusion toxin (e.g. abstract), and DT390 is an effective toxic molecule widely used in the art.

Debinski et al teach that a wide range of human cancers expressing IL-4 receptors (2nd member of the affinity pair), including T cell leukemia (malignant hematological disease), breast cancer, prostate cancer, and melanoma (table 1). They teach that such feature could be used for targeting toxins to the cancer cell (abstract). *Debinski et al* construct a plasmid vector comprising and expressing fusion protein of IL-4 and *Pseudomonas* exotoxin (PE, left column, page 14066).

Chan et al teach targeting a diphtheria toxin, DT_{390} to cancerous hematopoietic cells using IL-3. They teach a plasmid vector comprising and expressing fusion protein of IL-3 and DT_{390}.

Although *Debinski et al* and *Chan et al* do not teach using transfected cells for cancer therapy, the advantage of using transduced cells in place of targeted fusion toxin was taught by *Chen et al.*

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods as taught by *Chen et al* and *Kreitman et al,* by selecting an appropriate targeting molecule in the fusion toxin construct with a reasonable expectation of success. Given numerous targeting and toxic molecules known in the art as taught by *Chen et al, Kreitman et al, Chan et al*, and *Debinski et al*, given the numerous types of tumor cells and numerous receptors expressed on these cells, it is within the levels of the skilled

to select a proper targeting domain corresponding to a tumor cell of interest. Moreover, given the efficacy of the fusion toxins as taught by *Kreitman et al, Chan et al*, and *Debinski et al*, and the efficacy comparison as taught by *Chen et al*, the ordinary skilled would have had a reasonable expectation of success in using the transduced cells expressing the various immunotoxins. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Chen et al* (Nat 1997;385:78-80) and *Kreitman et al* (Int J Immunopharm 1992;14:465-72) as applied to claims 1, 2, 6, 9, 12, 15, 19-24, 34, 36-40, 42, 44, 46 above, and further in view of *Sweeney et al* (Bioconj Chem 1998;9:201-7).

The combined teaching of *Chen et al* and *Kreitman et al* does not explicitly teach using cytokines such as IL-7 as a targeting domain or treating hematological cancer. *Sweeney et al* supplemented the teaching of *Chen et al* and *Kreitman et al* by establishing that it is well known in the art that IL-7 could be effectively used to target a toxin to IL-7 bearing cells such as lymphoblastic leukemia cells, and illustrated selective cytotoxicity of the immunotoxin on IL-7 bearing cells (e.g. abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method as taught by *Chen et al* and *Kreitman et al* with that of *Sweeney et al,* by substituting the IL-6 as taught

by Kreitman et al with the IL-7 as taught by *Sweeney et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because given the numerous types of tumor cells and numerous receptors expressed on these cells, it is within the levels of the skilled to select a proper targeting domain corresponding to a tumor cell of interest. Given the efficacy of the targeting domains as taught by *Chen et al* and *Kreitman et al*, and the efficacy of the DAB389-IL-7 as taught by *Sweeney et al*, the ordinary skilled would have had a reasonable expectation of success in suppressing tumors with corresponding immunotoxin-expressing cells. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Chen et al* (Nat 1997;385:78-80) and *Kreitman et al* (Int J Immunopharm 1992;14:465-72) as applied to claims 1, 2, 6, 9, 12, 15, 19-24, 34, 36-40, 42, 44, 46 above, and further in view of *Heslop et al* (Curr Opin Hematol 1995;2:417-22).

The combined teaching of *Chen et al* and *Kreitman et al* does not explicitly teach viral vectors other than the retrovirus for transducing T cells. *Heslop et al* supplemented the teaching *Chen et al* and *Kreitman et al* by establishing that it was well known in the art at the time of the instant filing, improved vectors such as AAV and Adv are desired for transfecting different types of cells and for sustained high level expression of therapeutic genes (e.g. the section bridging pages 419-420).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods as taught by *Chen et al* and *Kreitman et al,* by selecting a proper vector for the fusion toxin construct with a reasonable expectation of success. Given numerous vectors known in the art as taught by *Heslop et al*, this limitation would fall within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

As an initial matter, during the telephone interview conducted on May 25, 2004, Applicant's representative presented an argument regarding the *Chen et al* reference. Applicant argued that *Chen et al* used NK cells, which is not T lymphocytes as claimed. However, a closer look at the *Chen et al* reference would find that *Chen et al* did use T lymphocytes rather than NK cells. "Tumor-specific killer cells" in the title of the *Chen* publication is just a custom name for the immunotoxin transduced T lymphocytes. Thus, the argument appears to be erred.

In the 6/7/04 response, Applicants argue that Chen reference does not suggest the use of T cells with significant binding affinity for cancer cells because it recommends against their use. Applicants further assert that complete absence of tumor specific T lymphocyte in *Chen* article indicates the lack of suggestion for the use of cancer-specific T lymphocytes.

The argument has been fully considered but found not persuasive because by reciting "THE DIFFICULTY IN OBTAINING TUMOR-SECIFIC CYTOTOXIC LYMPHOCYTES" (abstract), *Chen et al* implicitly teach the routing practice and desirability to use tumor-specific CTL for cancer therapy. It is only because the difficulty in obtaining such cells, they searched for a solution by artificially constructing tumor-specific killer cells using T cells. When viewing this teaching together with other references cited by *Chen et al* (Refs. 4-7), the reference teaching as a whole would have suggested to the ordinary skilled when there is difficulty to obtain sufficient amount of tumor-specific CTLs, the tumor-specific killer cells could be used. Accordingly, *Chen et al* do not teach away or recommend against the use of CTLs, but rather, provide an alternative supplementing the use of tumor-specific CTLs. Accordingly, the rejection is proper.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax

numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Q. Janice Li
Primary Examiner
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QL
September 30, 2004